REMARKS/ARGUMENTS

Interview request

Applicants respectfully request a telephonic interview after the Examiner has reviewed the instant response and amendment. Applicants request the Examiner call Applicants' representative, as noted below.

Status of the Claims

Pending claims

Claims 1, 46, 56-58, 61, 73, 125, 126, 130, 131, 133, 135, 137, 138, 140, 169, 171, 218, 221, 225, 229, 231-134, 236, 241, and 271-275, are currently pending.

Claims Withdrawn

Claims 73, 125, 126, 130, 131, 135, 137, 138, 140, 169, 171, 218, 221, 225, 229, 231-234, 236, 241, and 271-274, remain withdrawn as they are allegedly drawn to non-elected inventions.

Claims under examination

Claims 1, 46, 56-58, 61, 133, and 275 are currently under examination.

Outstanding Objections and Rejections to the Claims

Claims 133 and 275 are objected to for informalities. Claims 1, 46, 56-58, 61, and 133 are rejected under 35 U.S.C. § 112, first paragraph enablement and written description requirements.

Applicants, respectfully traverse all outstanding objections and rejections to the claims.

Support for the claim amendments

The specification sets forth an extensive description of the invention in the amended claims. Accordingly, Applicants aver that no new matter has been added in the instant amendment.

Claim Objections

Claim 133 is objected to as allegedly being dependent upon non-elected subject matter. Claim 275 is objected to as allegedly being unclear. The instant amendment addresses these issues.

Applicants note that after the elected product claims (Group I, including claim 133) are found allowable, the withdrawn process claims (Groups II-XXII), that depend from or otherwise require all the limitations of an allowable product claim should be rejoined. MPEP § 821.04; In re Ochiai, 37 USPQ2d 1127 (Fed. Cir. 1995); In re Brouwer, 37 USPQ2d 1663 (Fed. Cir. 1995; 1184 OG 86, 3/26/96.

Issues under 35 U.S.C. §112, first paragraph

Enablement

Claims 1, 46, 56-58, 61, and 133, are rejected under 35 U.S.C. § 112, first paragraph enablement requirement for the reasons stated on pages 4-11, of the OA.

The Patent Office states that the specification is enabling for the polypeptide of SEQ ID NO:7 encoding the polypeptide of SEQ ID NO:8 having glucoamylase activity, or a polynucleotide sequence that hybridizes under defined stringent conditions to the full-length complement of SEQ ID NO:7 and encodes a polypeptide with glucoamylase activity, isolated host cells comprising the polynucleotide and a micro-array comprising said polynucleotide. However, it is alleged that the specification does not provide enablement for any isolated polynucleotide having at least 95% nucleic acid sequence identity with the polynucleotide sequence of SEQ ID NO:7 encoding a polypeptide having glucoamylase activity or a nucleic acid probe comprising at least 70 consecutive bases of SEQ ID NO:7. Further, the Office alleges that undue experimentation would be required to practice the claimed invention. The Office discusses its reasoning in light of the factors to be used for determining undue experimentation as set forth in In re Wands:

The breadth of the claims

To address the Office's concerns about the size of the genus, the claims have been amended to clearly indicate the stringent hybridization conditions under which the probe binds to the identified nucleic acid. Further, the identified nucleic acid has been limited to only nucleic acids having at least 95% sequence identity to SEQ ID NO:7 and wherein the identified nucleic

acid has glucoamylase activity.

The Office alleges that Applicants have not provided sufficient guidance regarding which changes can be made to a protein's amino acid sequence, or to the polynucleotide's respective codons, while retaining glucoamylase activity. The Office further alleges that undue experimentation would be required of the skilled artisan to make and use the claimed polynucleotides. Applicants respectfully disagree.

It is alleged that the specification fails to provide any guidance with regard to the making of variants and mutants. Further, the Office alleges that the specification lacks working examples and that the unpredictability of the art precludes predicting function from a polypeptide primary structure. The Office further alleges that without such guidance, one of ordinary skill in the art would be reduced to producing and testing all of the virtually infinite number of variants.

The Office also cited art, specifically Guo et al., to support its *prima facie* case of lack of enablement alleging, inter alia, that it was not routine to screen for multiple substitutions or multiple modifications of the exemplary sequence to determine the additional species within the scope of the claimed genus. The Office uses Guo to support the allegation that because there is a large number of possible nucleic acid sequence variations, it would take undue experimentation to determine all of the active, versus inactive, species within the claimed genus (that are variants of the exemplary SEQ ID NO:7).

In order to make an enablement rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. See also MPEP §2164.04, 8th ed., rev. July 2008.

Applicants respectfully aver that Guo is not sufficient to rebut the instant application's presumption of enablement and therefore cannot support a *prima facie* case of lack of enablement. Guo developed a mathematical paradigm to quantitate protein tolerance to random

sequence changes. Guo's model was developed to understand the probability that a random amino acid replacement will lead to a protein's functional inactivation. While Guo's model does predict that random codon replacement will generate many inactive variants, in fact, they found 920 "tolerated" or active variants. Thus, Guo actually demonstrates that significant numbers of active variants can be generated using a random mutation and screening protocol. As such, Guo is not sufficient to rebut the presumption of enablement.

The Office acknowledged that methods of producing variants of a known sequence are well known to the skilled artisan. However, it is alleged that without sufficient guidance, the skilled artisan would be reduced to the necessity of producing and testing virtually infinite possibilities of variants to determine which ones have glucoamylase activity. Applicants respectfully disagree. Procedures for identifying polypeptides having glucoamylase activity were conventional and routine in the art at the time of the invention. Further, exemplary assays for identifying polypeptides having glucoamylase activity are described, inter alia, on page 65, paragraph [0482] of the specification. Specifically, after a starch is liquefied with an amylase, the liquefied starch is then saccharified with a glucoamylase, e.g. a glucoamylase of the invention. DE (Dextrose Equivalent) of the saccharified sample can then be measured, as described in paragraph [0482], to determine the effectiveness of the added glucoamylase. Further, the specification provides guidance on making variants which require no structural or functional knowledge of the starting protein. Specifically, see e.g., page 14, paragraph [0127], which expressly sets forth which conservative amino acid substitutions can be made to the exemplary SEQ ID NO:8 to make a variant glucoamylase within the scope of the invention.

Additionally, whether large numbers of compositions (e.g., variant glucoamylases) must be screened to determine if one can be used to practice the claimed invention is irrelevant to an enablement inquiry. Enablement is not precluded by the necessity to screen large numbers of compositions, as long as that screening is "routine," i.e., not "undue," to use the words of the Federal Circuit. The Federal Circuit in In re Wands directed that the focus of the enablement inquiry should be whether the experimentation needed to practice the invention is or is not "undue" experimentation. Guidance as to how much experimentation may be needed and still not be "undue" was set forth by the Federal Circuit in, e.g. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987), which was discussed in Applicants' response of July 17, 2003.

The proper legal test is that the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. See, e.g., In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). See MPEP §2164.08, 8th ed., rev. July 2008. `The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.' " In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)). MPEP §2164.06, 8th ed., rev. July 2008. As the proper legal test is that the scope of enablement must only bear a "reasonable correlation" to the scope of the claims, methods for making the claimed genus of glucoamylase polypeptides are sufficiently enabling if a reasonable number of claimed species are successfully made by protocols known in the art and/or described in the specification. Protocols for glucoamylase activity screening were well known in the art at the time of the invention. Thus, using the teaching of the specification and other protocols known in the art at the time of the invention, one skilled in the art could have successfully practiced the invention without undue experimentation, including making and using the claimed genus of glucoamylase-encoding polypeptides without undue experimentation. In other words, methods for making and screening for glucoamylases were sufficiently sophisticated and well known at the time of the invention that one of skill in the art could have made the claimed genus of glucoamylase polynucleotides without "undue experimentation".

As the specification provided direction and guidance on how to practice the claimed invention and all of the methods needed to practice the invention were well known, and there was a high level of skill in the art at the time the application was filed, the instant specification did provide reasonable enablement commensurate with the scope of the claimed invention. Accordingly, the enablement rejection under section 112, first paragraph, can be properly withdrawn.

Written Description

Claims 1, 46, 56-58, 61, and 133, are rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement and containing subject matter not described in the specification in such a way as to reasonably convey to one of skill in the art that the inventor had possession of the claimed invention. Applicants respectfully aver

that the claimed invention is sufficiently described in the specification such that one of ordinary skill in the art would be able to ascertain the scope of the claims with reasonable clarity and recognize that Applicants' were in possession of the claimed invention at the time of filing.

The Office is concerned that the claims are directed to any isolated polynucleotide having at least 95% nucleic acid sequence identity with the polynucleotide sequence of SEQ ID NO:7 encoding a polypeptide having glucoamylase activity or a nucleic acid probe comprising at least 70 consecutive bases of SEQ ID NO:7. The Office alleges that Applicants disclose the structure of only a single species of the recited genus of polynucleotides encoding a polypeptide having glucoamylase activity, while providing no guidance which structural elements or functional activity the members of the genus of variants of the polynucleotide of SEQ ID NO:7 are required to have. The Office further alleges that neither the specification nor the art teach the correlation between structure and the desired glucoamylase activity.

Applicants respectfully aver that all polynucleotides of the claimed invention are clearly described by structure (the exemplary SEQ ID NO:7, encoding SEQ ID NO:8), a physico-chemical property (polynucleotides having at least 95% sequence identity to SEQ ID NO:7) and function (glucoamylase activity). Applicants respectfully submit that describing a genus of polynucleotides in terms of physico-chemical properties (polynucleotides having at least 95% sequence identity to SEQ ID NO:7) and function (e.g., encoding glucoamylases) satisfies the written description requirement of section 112, first paragraph, as recognized by the USPTO guidelines.

Additionally, Applicants' respectfully aver that it was not necessary for one skilled in the art to know the correlation between structure and function of glucoamylases to be in possession of the invention. One of ordinary skill in the art, using the teaching of the specification, would have been able to make and screen for nucleic acids that encode for variants having at least 95% sequence identity to SEQ ID NO:7. For example, using the specification and the knowledge of one of skill in the art, variant nucleic acids having codon changes for one or more conservative amino acid substitutions to SEQ ID NO:8, could be made and then those nucleic acids could be expressed and screened using routine screening methods to determine, with predicable positive results, which of those nucleic acids encode for a polypeptide having glucoamylase activity. One of ordinary skill in the art using the teaching of the specification would have been able to ascertain what polynucleotides encoding polypeptides having conservative amino acid

substitutions, were within the scope of the claims with reasonable clarity to recognize that Applicants' were in possession of the claimed invention at the time of filing.

The Patent Office cites Witkowski et al., Seffernick et al., and Broun et al to show how even small changes in structure can lead to changes in activity. Witkowski showed that a small number of amino acid residue changes in the catalytic site of a family of structurally related enzymes can result in a change in activity. Witkowski noted that beta-ketoacyl synthases involved in the biosynthesis of fatty acids and polyketides exhibit extensive sequence similarity and share a common reaction mechanism. Interestingly, Witkowski also noted that multiple sequence alignments identified catalytic sites and provided the first clues about the possible identities of residues that play critical roles in catalysis. In fact, Witkowski's data suggests that most changes in an enzyme's amino acid sequence (*e.g.*, non-catalytic site amino acid residues) are not important in determining, or changing, its catalytic specificity. Thus, while this reference may show that one single conservative substitution can have a major impact in enzymatic activity, Witkowski's data actually indicates that most changes in an enzyme's amino acid sequence (*e.g.*, non-catalytic site amino acid residues) are not important in determining, or changing, its catalytic specificity.

In regard to Seffernick et al., also cited by the Office in support of its written description argument, Seffernick compared a deaminase (melamine deaminase) with a hydrolase (atrazine chlorohydrolase, AtzA) and found that each enzyme consists of 475 amino acids and differs by only 9 amino acids. Seffernick opined that their data suggest that the 9 amino acid differences between melamine deaminase and AtzA represent a short evolutionary pathway connecting enzymes catalyzing physiologically relevant deamination and dehalogenation reactions. As with Witkowski, Seffernick's data suggest that most changes in an enzyme's amino acid sequence (e.g., non-catalytic site amino acid residues) are not important in determining, or changing, its catalytic specificity.

Broun et al. (1998) Science 282:1315-1317, shows that a small number of amino acid reside changes in the catalytic site of a family of structurally related enzymes can result in a change in activity (in particular, Broun found that as few as four amino acid substitutions can convert an oleate 12-desaturase to a hydroxylase and as few as six result in conversion of a hydroxylase to a desaturase). However, in Broun, there is no discussion regarding the merits or difficulties of protocols that screen for enzyme activity, e.g., screen for enzyme activity in a

library of polypeptides expressed by a plurality of nucleic acid variants. In fact, it appears that Broun considered screening for enzyme activity in their enzyme variants a routine process. There is no discussion on whether changes in non-catalytic site amino acid residues have any effect on enzyme activity. In fact, Broun's data suggest that most changes in an enzyme's amino acid sequence (e.g., non-catalytic site amino acid residues) are not important in determining, or changing, its catalytic specificity.

Accordingly, Applicants respectfully submit that the pending claims meet the written description requirement under 35 U.S.C. §112, first paragraph. In light of the above remarks, Applicants respectfully submit that amended claims are sufficiently described in the specification to overcome the written description rejection based upon 35 U.S.C. §112, first paragraph.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully aver that the Examiner can properly withdraw the objections and the rejections of the pending claims under 35 U.S.C. § 112, first paragraph. Applicants respectfully submit that after entry of the instant amendment all claims pending in this application will be in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. **50-0661** referencing docket no. **D1530-9N**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

As noted above, Applicants have requested a telephone conference with the undersigned representative to expedite prosecution of this application. After the Examiner has reviewed the instant response and amendment, please telephone the undersigned at (858) 526-5450.

Dated: November 20, 2009

Respectfully submitted,

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